WHAT IS CLAIMED IS:

1. A method for sequencing a target nucleic acid, said method comprising:

(a) combining:

(i) a substrate comprising an array of chemically synthesized and positionally distinguishable oligonucleotides each of which binds to a defined subsequence of preselected length; and

(ii) a target nucleic acid; thereby forming target-oligonucleotide hybrid complexes of complementary subsequences of known sequence;

(b) contacting said target-oligonucleotide hybrid complexes with a nuclease; thereby removing target-oligonucleotide complexes which are not perfectly complementary; and

(c) determining which of said oligonucleotides have specifically interacted with subsequences in said target nucleic acid.

2. The method as recited in claim 1 wherein said array of oligonucleotides recognizes substantially all possible subsequences of preselected length found in said target nucleic acid.

3. The method as recited in claim 1 wherein each oligonucleotide is of a length between about 6 and 20 bases.

4. The method as recited in claim 1 wherein each oligonucleotide is of a length between about 8 and 15 bases.

5. The method as recited in claim 1 wherein said array of oligonucleotides comprises about 1,000 different oligonucleotides.

6. The method as recited in claim 1 wherein said array of oligonucleotides comprises about 3,000 different oligonucleotides.

7. The method as recited in claim 1 wherein said array of oligonucleotides comprises about 10^4 different oligonucleotides.

8. The method as recited in claim 1 wherein said array of oligonucleotides comprises about 10^5 different oligonucleotides.

9. The method as recited in claim 1 wherein said array of oligonucleotides comprises about 10^6 different oligonucleotides.

10. The method as recited in claim 1 wherein said target nucleic acid is ribonucleic acid (RNA).

11. The method as recited in claim 10 wherein said nuclease in an RNA nuclease.

12. The method as recited in claim 11 wherein said RNA nuclease is RNase A.

13. The method as recited in claim 1 wherein said target nucleic acid is deoxyribonucleic acid (DNA).

14. The method as recited in claim 13 wherein said nuclease is a DNA nuclease.

15. The method as recited in claim 14 wherein said DNA nuclease is S1 nuclease.

16. The method as recited in claim 14 wherein said DNA nuclease is Mung Bean nuclease.

17. A method for sequencing a target nucleic acid, said method comprising:

(a) combining:

(i) a substrate comprising an array of chemically synthesized and positionally distinguishable oligonucleotides each of which binds to a defined subsequence of preselected length; and

(ii) a target nucleic acid which is longer than each of said probes; thereby forming target-oligonucleotide hybrid complexes of complementary subsequences of known sequence with a 3' target overhang;

(b) contacting said target-oligonucleotide hybrid complexes with a ligase and a labelled, ligatable oligonucleotide probe;

(c) removing said target nucleic acid and labelled, unligatable oligonucleotide probes; and

(d) determining which of said oligonucleotides contain said labelled, ligatable oligonucleotide probe as an indication of a subsequence which is perfectly complementary to a subsequence of said target nucleic acid.

18. The method as recited in claim 17 wherein said ligase is DNA T4 ligase.

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SEQUENCING BY HYBRIDIZATION ON HIGH DENSITY PROBE ARRAYS: ENZYMATIC DISCRIMINATION ENHANCEMENT

ABSTRACT OF THE DISCLOSURE

The present invention provides improved methods for discriminating between fully complementary hybrids and those that differ by one or more base pairs. In one embodiment, the present invention provides methods of using nuclease treatment to improve the quality of hybridization signals on high density oligonucleotide arrays.

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